



Cancer Hallmarks: An Approach to Understanding the Biology of Tumorigenesis

Dean W. Felsher, MD PhD

Professor of Medicine-Oncology and Pathology

Director of Oncology Research

Director of Translational Research and Applied Medicine

Director of Admissions Medical Scientist Training

Co-Director Cancer Nanotechnology

Director Advanced Residency Training

Converging on Cancer Workshop

NIEHS May 28-30, 2019

Stanford University

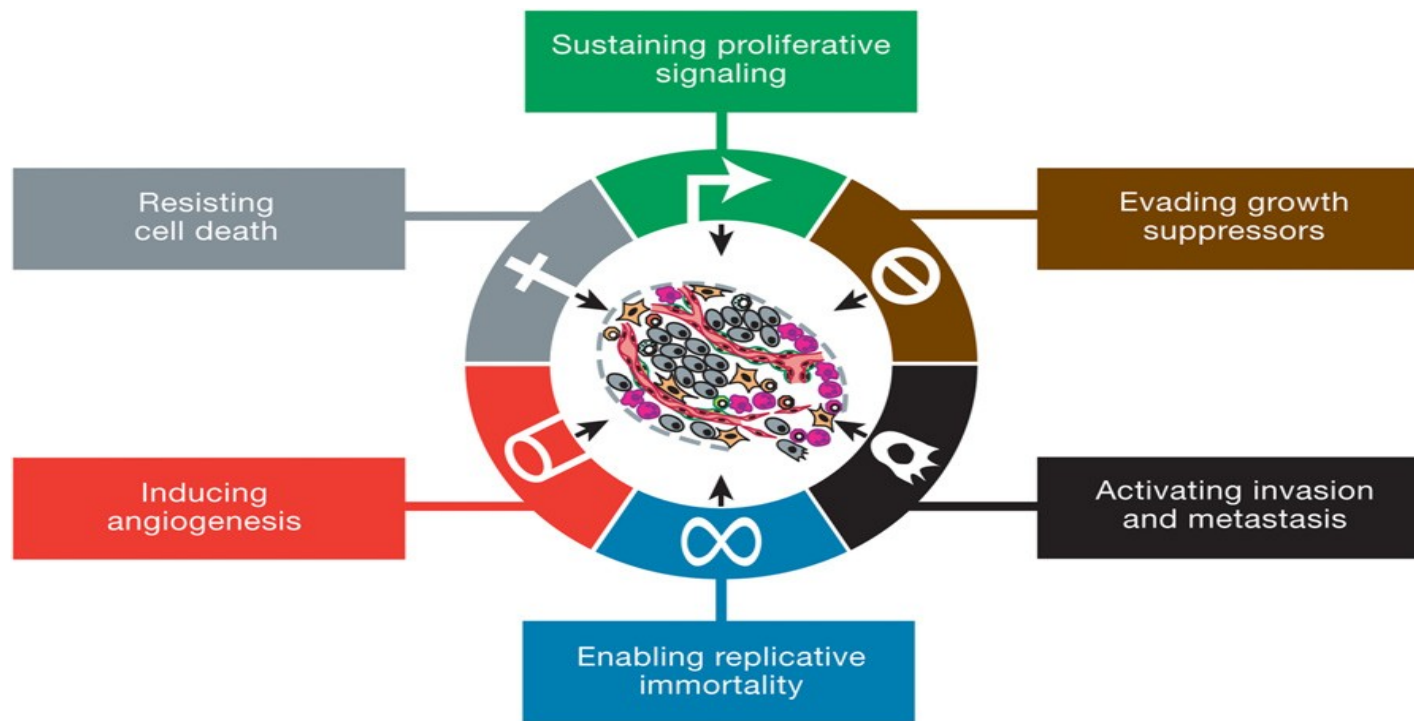
Outline of Presentation

- Cancer Hallmarks: Original and Emerging
- Cancer Hallmarks and Carcinogenesis
- Cancer Hallmarks: Cancer Prevention and Treatment
- Cancer Hallmarks: Their Measurement

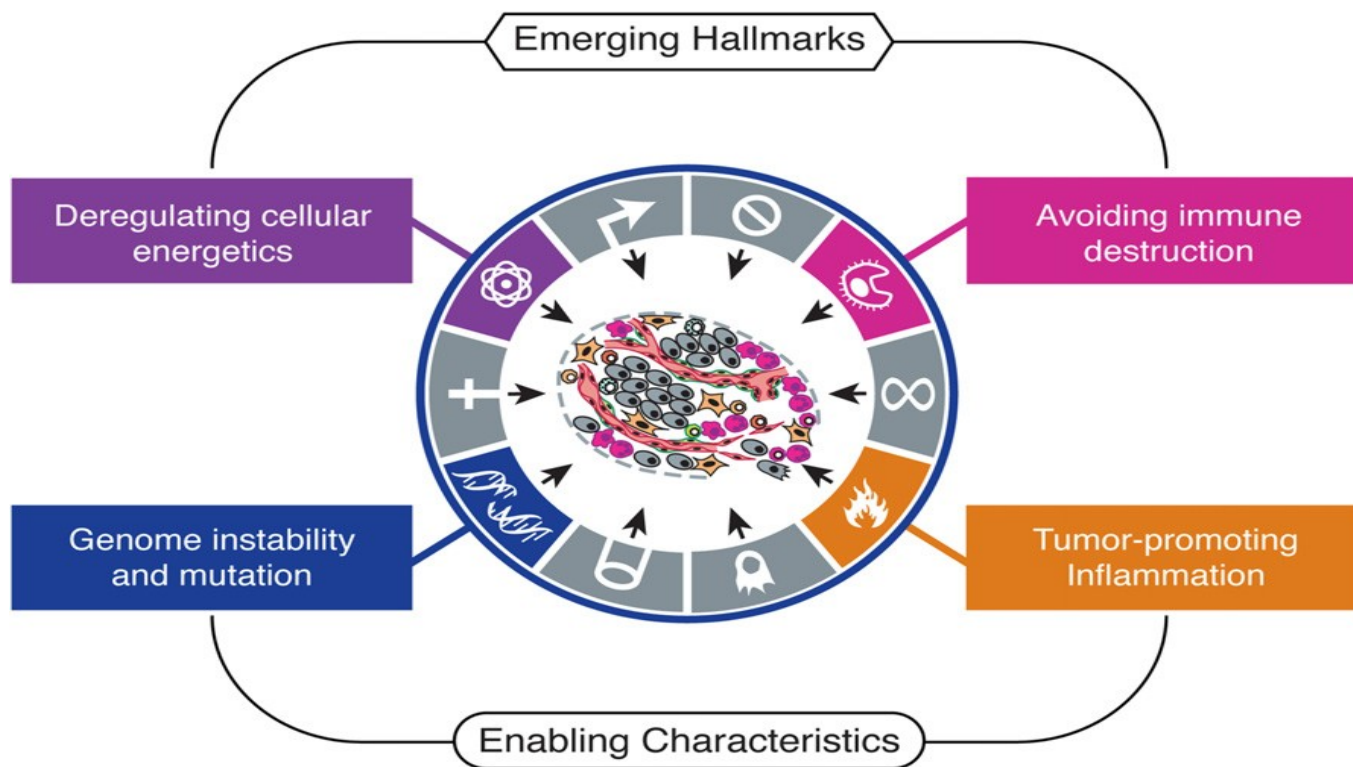
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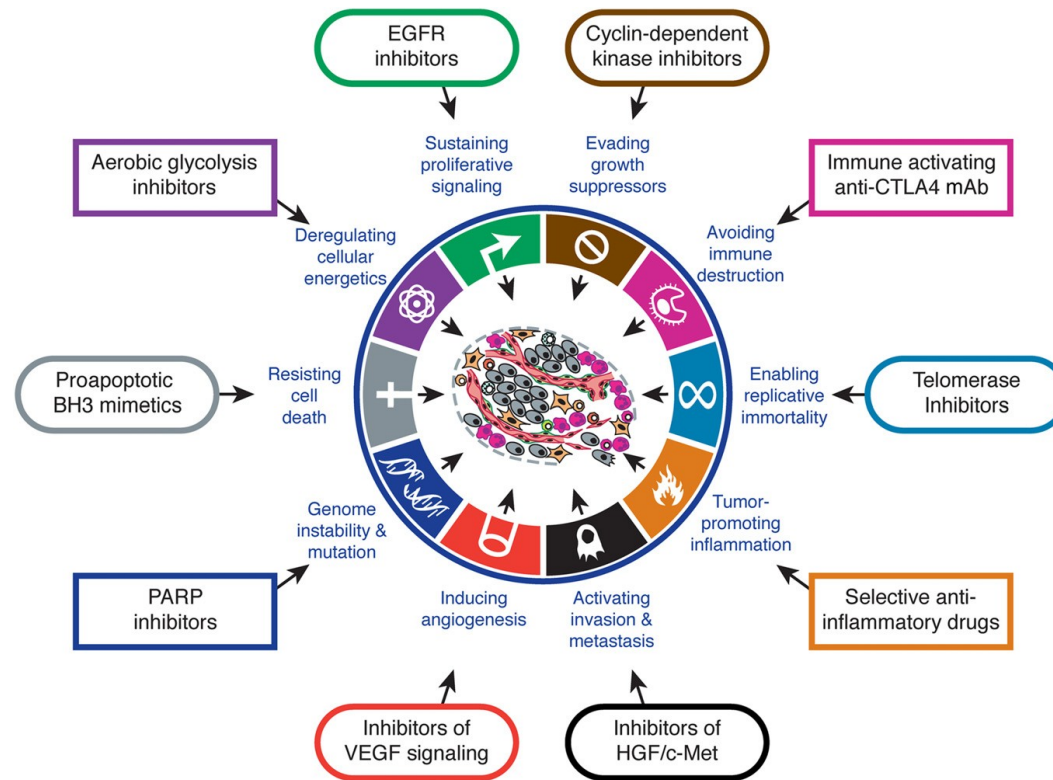
Original Cancer Hallmarks



Emerging Cancer Hallmarks



Cancer Hallmarks



Outline of Presentation

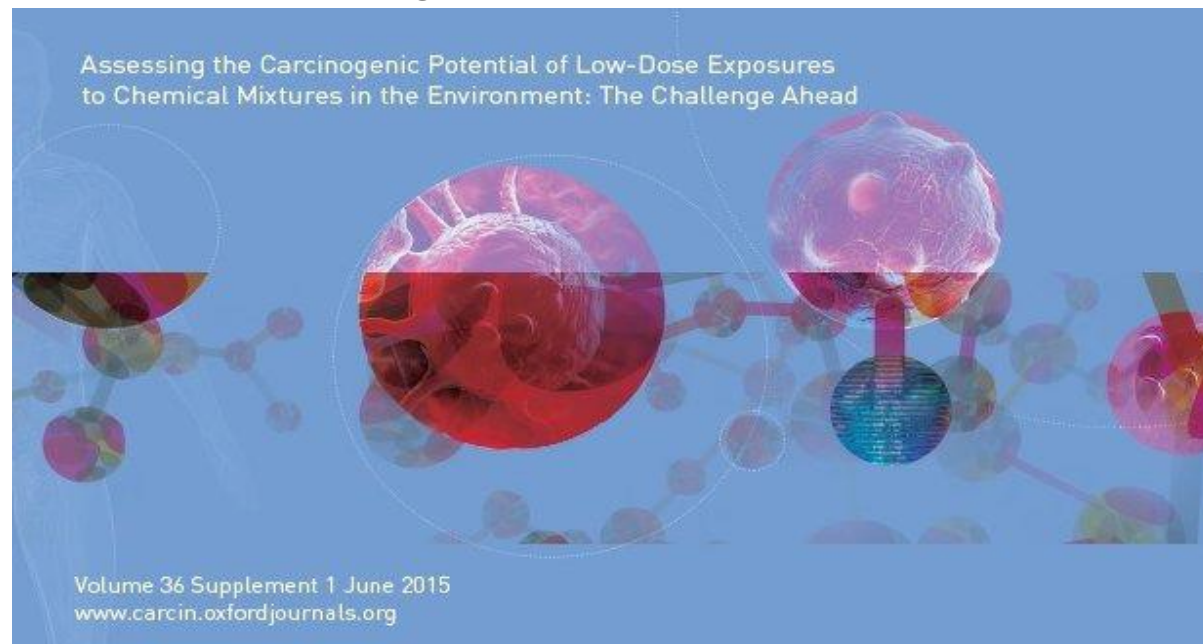
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Cancer Hallmarks and Carcinogenesis

Leroy Low and Halifax Project

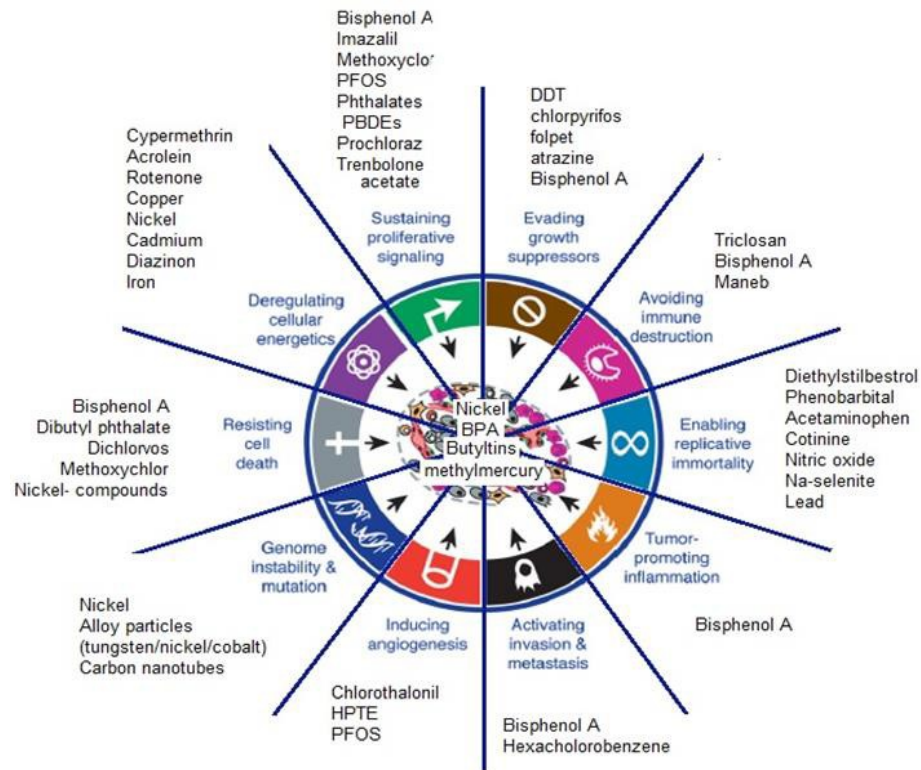
Goodson et al, Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead

Carcinogenesis, 2015, Vol 36, Suppl 1



Cancer Hallmarks and Carcinogenesis

Leroy Low and Halifax Project



REVIEW

The effect of environmental chemicals on the tumor microenvironment

Stephanie C. Casey, Monica Vaccari¹, Fahd Al-Mulla², Rabeah Al-Temaimi³, Amedeo Amedei³, Mary Helen Barcellos-Hoff⁴, Dustin G. Brown⁵, Marion Chapellier⁶, Joseph Christopher⁷, Colleen Curran⁸, Stefano Forte⁹, Roslida A. Hamid¹⁰, Petr Heneberg¹¹, Daniel C. Koch, P.K. Krishnakumar¹², Ezio Laconi¹³, Veronique Maguer-Satta⁶, Fabio Marongiu¹³, Lorenzo Memeo¹⁴, Chiara Mondello¹⁵, Jayadev Raju¹⁶, Jesse Roman¹⁷, Rabindra Roy¹⁸, Elizabeth P. Ryan⁶, Sandra Ryeom¹⁹, Hosni K. Salem²⁰, A. Ivana Scovassi¹⁵, Neetu Singh²¹, Laura Soucek²², Louis Vermeulen²³, Jonathan R. Whitfield²², Jordan Woodrick¹⁸, Annamaria Colacci¹, William H. Bisson²⁴ and Dean W. Felsher^{25,*}

Division of Oncology, Departments of Medicine and Pathology, Stanford University, Stanford, CA 94305, USA, ¹Center for Environmental Carcinogenesis and Risk Assessment, Environmental Protection and Health Prevention Agency, 40126 Bologna, Italy, ²Department of Pathology, Kuwait University, 13110 Safat, Kuwait, ³Department of Experimental and Clinical Medicine, University of Firenze, 50134 Florence, Italy, ⁴Department of Radiation Oncology, NYU School of Medicine, New York, NY 10016, USA, ⁵Department of Environmental and Radiological Health Sciences, Colorado State University/ Colorado School of Public Health, Fort Collins, CO 80523-1680, USA, ⁶Centre De Recherche En Cancérologie De Lyon, U1052-UMR5286, Université de Lyon, 69007 Lyon, France, ⁷Cancer Research UK, Cambridge Institute, University of Cambridge, Robinson Way, CB2 0RE Cambridge, UK, ⁸School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53705, USA, ⁹Mediterranean Institute of Oncology, 95029 Viagrande, Italy, ¹⁰Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, 43400 Selangor, Malaysia, ¹¹Charles University in Prague, Third Faculty of Medicine, 100 00 Prague 10, Czech Republic, ¹²Center for Environment and Water, Research Institute, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia, ¹³Department of Science and Biomedical Technology, University of Cagliari, 09124 Cagliari, Italy, ¹⁴Pathology Unit, Mediterranean Institute of Oncology, 95029 Viagrande, Italy, ¹⁵Institute of Molecular Genetics, National Research Council, 27100 Pavia, Italy, ¹⁶Regulatory Toxicology Research Division, Bureau of Chemical Safety Food Directorate, Health Products and Food Branch Health Canada, Ottawa, Ontario K1A0K9, Canada, ¹⁷Department of Medicine, University of Louisville, Louisville, KY 40202, USA, ¹⁸Molecular Oncology Program, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington DC 20057, USA, ¹⁹University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA, ²⁰Urology Department, Kasr Al-Ainy School of Medicine, Cairo University, El Manial, Cairo 11562, Egypt, ²¹Centre for Advanced Research, King George's Medical University, Chowk, Lucknow, Uttar Pradesh 226003, India, ²²Vall d'Hebron Institute of Oncology (VHIO) and Institut Catalana de Recerca i Estudis Avançats (ICREA), 08035 Barcelona, Spain, ²³Center for Experimental Molecular Medicine (CEMM), Academic Medical Center (AMC), Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands, ²⁴Department of Environmental and Molecular Toxicology, Environmental Health Sciences Center, Oregon State University, Corvallis, OR 97331, USA, and ²⁵Division of Oncology, Departments of Medicine and Pathology, Stanford University, Stanford, CA 94305, USA

*To whom correspondence should be addressed. Tel: +1 650 725 6454; Fax: +1 650 725 1420; Email: dfelshe@stanford.edu

Correspondence may also be addressed to William H. Bisson. Tel: +1 541 737 5735; Fax: +1 541 737 0497; Email: bissonw@science.oregonstate.edu

Downloaded from <http://carcin.oxfordjournals.org/> at Oxford Journals on July 14, 2015

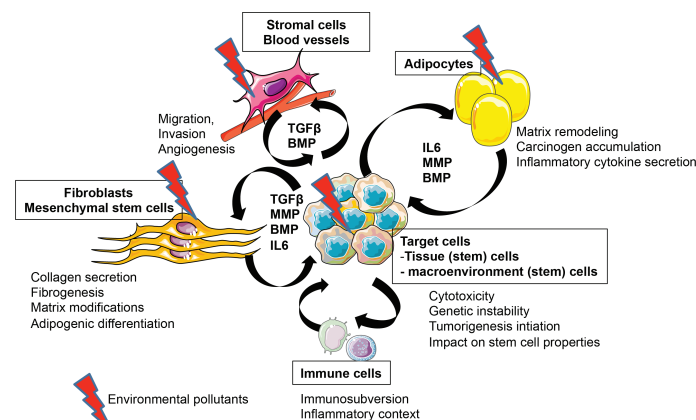


Figure 2. Environmental pollutant target resident cells and their local environment thus affecting key parameters of tissue homeostasis. Environmental pollutants target tissue resident cells, thus changing their intrinsic properties, and also affect their environment, in particular changing soluble factors available. All these events can lead to modifications of tissue homeostasis and emergence of cancer. During our lifetime, we can be exposed to different types of carcinogens at different times and the consequences of combinatorial exposure remain poorly deciphered. Environmental pollutant seems to induce both short- and long-term effects, which together with our own history (aging, genetic predisposition and/or cancer history) creates a context that may promote the development of cancer, long after the initial parameters. All these complex and person-dependent parameters raise challenging issues for public health to overcome cancer induced by carcinogens.



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

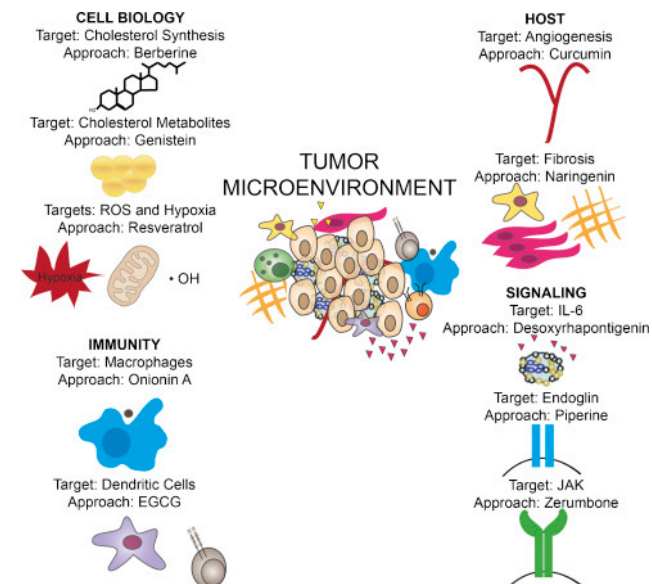


Review

Cancer prevention and therapy through the modulation of the tumor microenvironment



Stephanie C. Casey^a, Amedeo Amedei^b, Katia Aquilano^c, Asfar S. Azmi^d, Fabian Benencia^e, Dipita Bhakta^f, Alan E. Bilsland^g, Chandra S. Boosani^h, Sophie Chenⁱ, Maria Rosa Ciriolo^c, Sarah Crawford^j, Hiromasa Fujii^k, Alexandros G. Georgakilas^l, Gunjan Guha^f, Dorota Halicka^m, William G. Helferichⁿ, Petr Heneberg^o, Kanya Honoki^k, W. Nicol Keith^g, Sid P. Kerkar^p, Sulma I. Mohammed^q, Elena Niccolai^r, Somaira Nowsheen^s, H.P. Vasantha Rupasinghe^t, Abbas Samadi^u, Neetu Singh^v, Wamidh H. Talib^w, Vasundara Venkateswaran^x, Richard L. Whelan^y, Xujuan Yangⁿ, Dean W. Felsher^{a,*}



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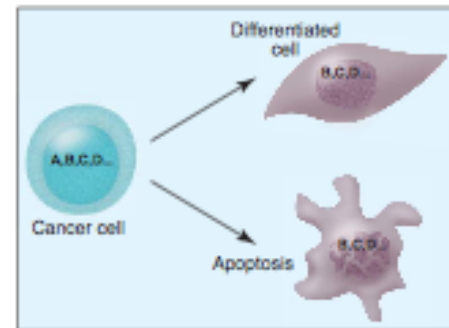
Oncogene Addiction



Bernard Weinstein, MD

PERSPECTIVES: CANCER

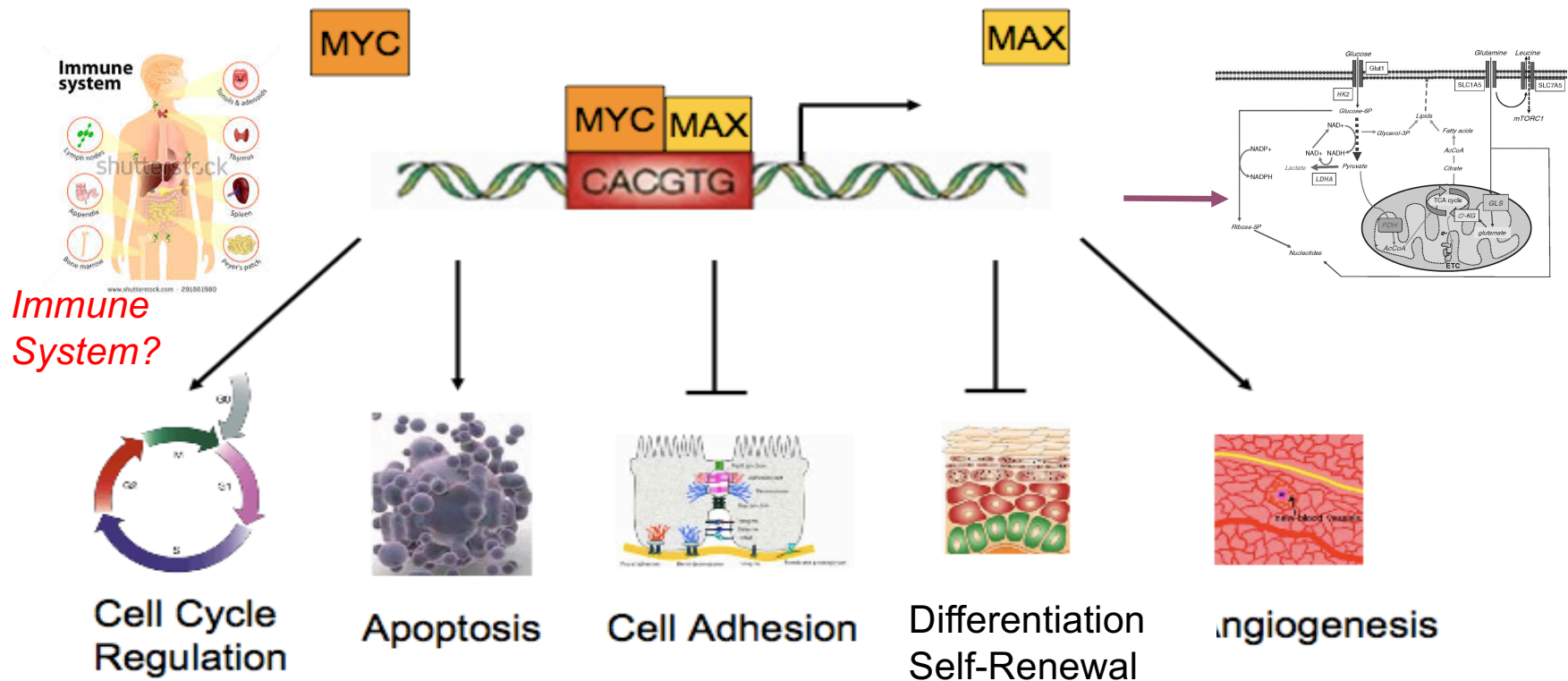
Addiction to Oncogenes—the Achilles Heal of Cancer



A one-step remedy. Cancer cells acquire abnormalities in multiple oncogenes and tumor suppressor genes (A, B, C, and D). Inactivation of a single critical oncogene (A) can induce cancer cells to differentiate into cells with a normal phenotype or to undergo apoptosis. This dependence on (addiction to) A for maintaining the cancer phenotype provides an Achilles heel for tumors that can be exploited in cancer therapy.

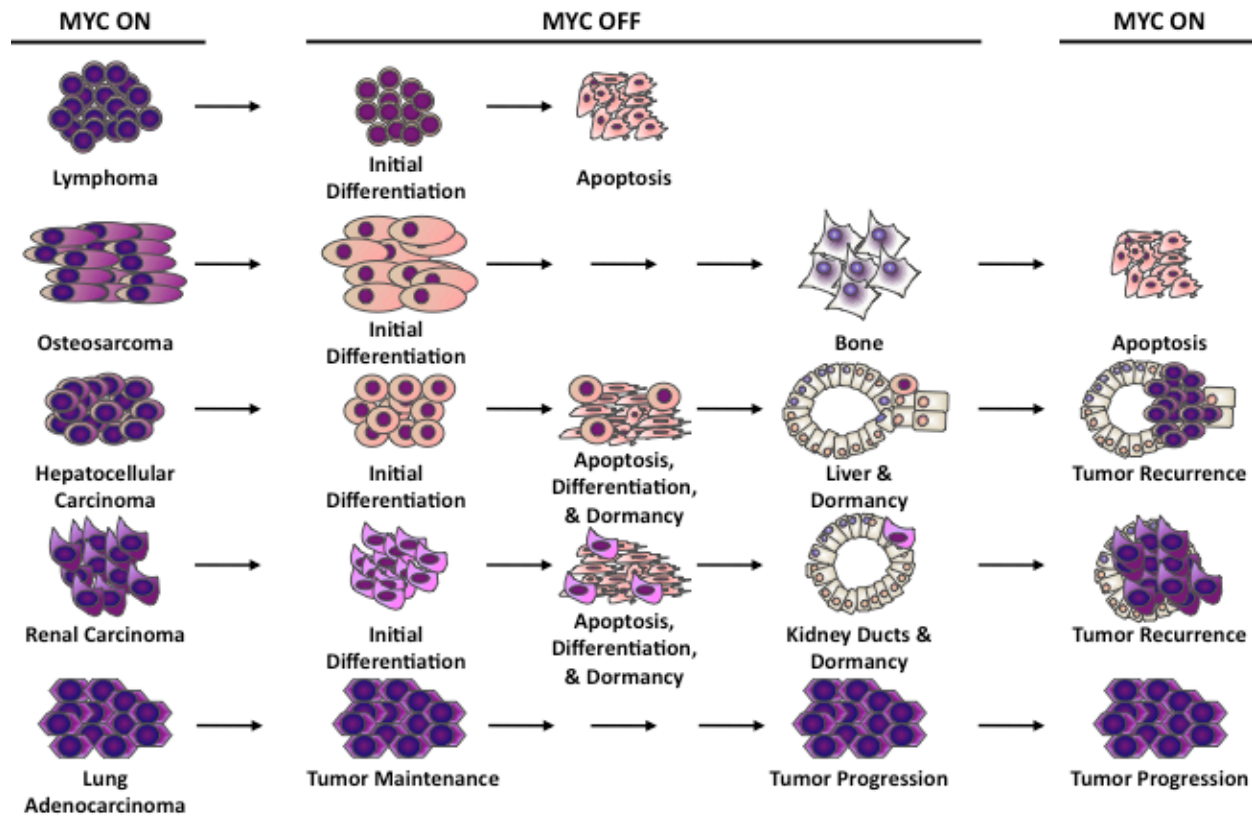
Jain and Felsner, Science, 2002

Cellular functions of MYC



Adapted from Boxer and Dang, 2001; Perengieris et. al., 2002

MYC INDUCED TUMORS ARE ONCOGENE ADDICTED



Molecular Cell 1999

Science 2002

Nature 2004

PNAS 2015

Sci Trans Med 2014

Mechanisms of Oncogene Addiction

- Tumor Cell Intrinsic

Proliferation and Apoptosis

[Molecular Cell, 1999; Science, 2002; Nature Medicine, 2009;
Sci Trans Med 2011; PNAS, 2012, PNAS; 2014 Oncotarget, 2016]

Differentiation [Nature, 2004; PLoS Biology 2004]

Self-Renewal/Senescence [PNAS 2006; Cancer Cell, 2014]

Metabolism and Ribosomal Biogenesis [PloS Gen 2008; Nat Rev Can 2010;
PNAS 2014; PNAS 2015, PNAS 2017]

Epigenetic Programs [Cancer Cell, 2014]

- Tumor Microenvironment and Host Immune System

Angiogenesis [PNAS, 2007]

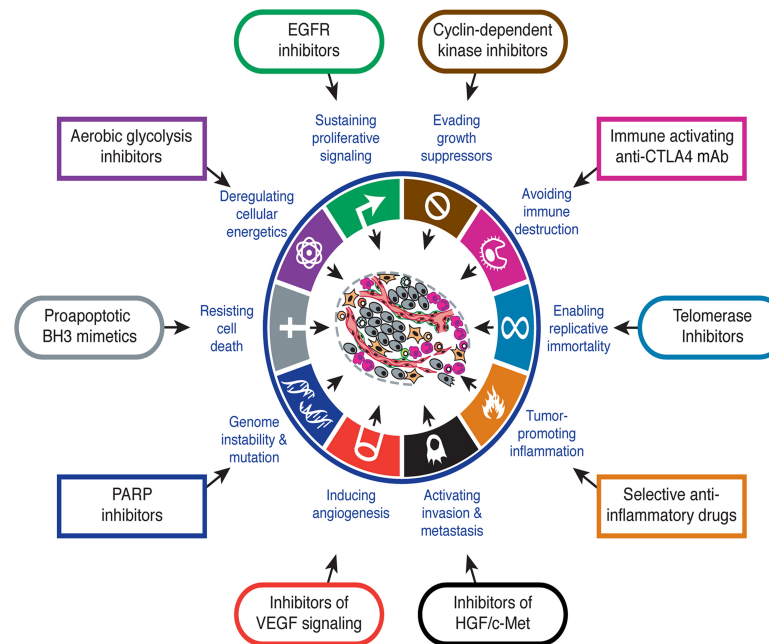
Autocrine/TGF-beta [Genes and Development, 2010]

Immune/CD4+ T-cells [Cancer Cell 2010] [SITC 2015]

Immune Checkpoints [Science 2016]

d the “Hallmarks of Cancer”

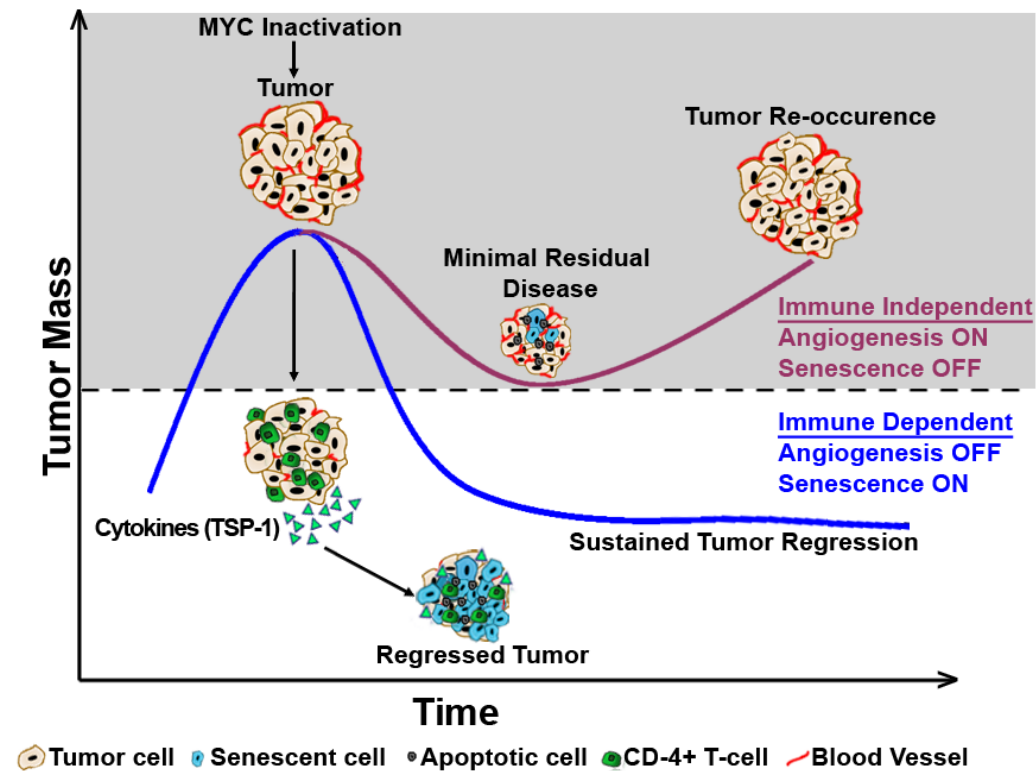
MYC —



Meital. Li and Felsher, CSHL Press, 2014

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Immune System Essential to Elicit Oncogene Addiction

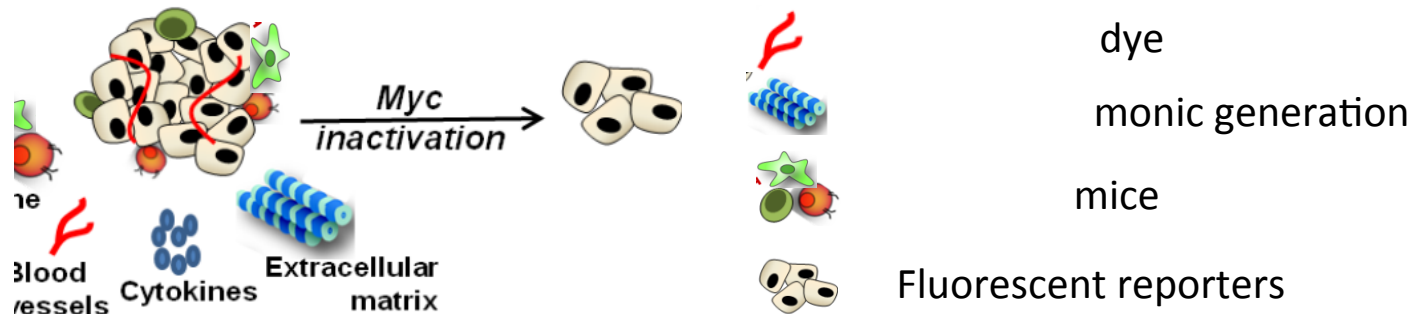


Rakhra et al, Cancer Cell, 2010

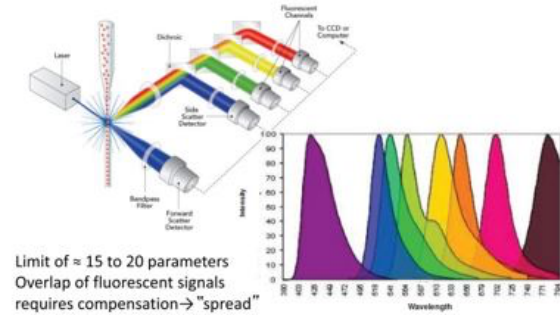
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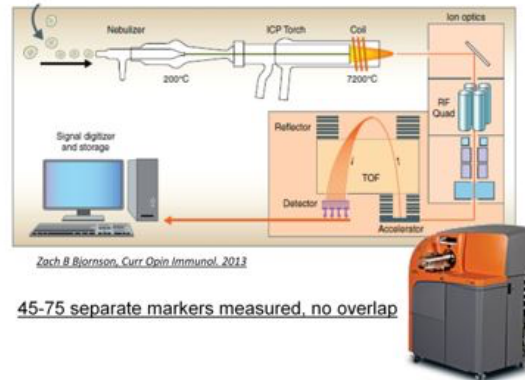
Real-time In Vivo Imaging: IVM



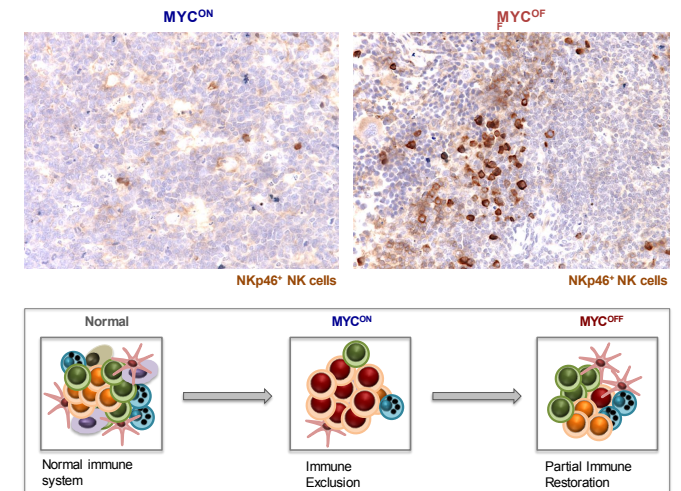
Flow Cytometry



CyTOF (Cytometry by Time Of Flight)



MYC oncogene promotes NK exclusion



Swaminathan, Heftdal, Liefwalker and Felsher, *in revision*

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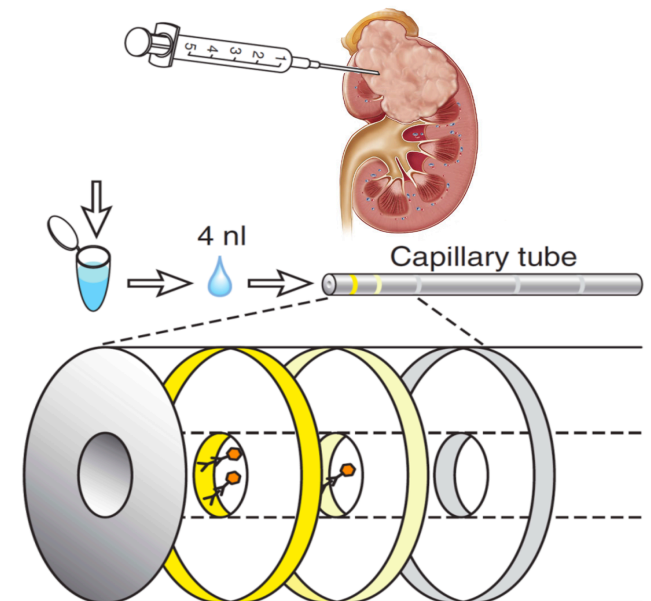
A Tractable Approach: Nanoscale Proteomic Analysis:
Interrogating action of therapeutics in clinical specimens in real-time

TECHNICAL REPORTS

nature
medicine

Nanofluidic proteomic assay for serial analysis of
oncoprotein activation in clinical specimens

Alice C Fan¹, Debabrita Deb-Basu², Mathias W Orban¹, Jason R Gotlib³, Yasodha Natkunam⁴, Roger O'Neill²,
Rose-Ann Padua⁵, Liwen Xu¹, Daryl Taketa², Amy E Shirer¹, Shelly Beer¹, Ada X Yee¹, David W Voehringer² &
Dean W Felsher¹

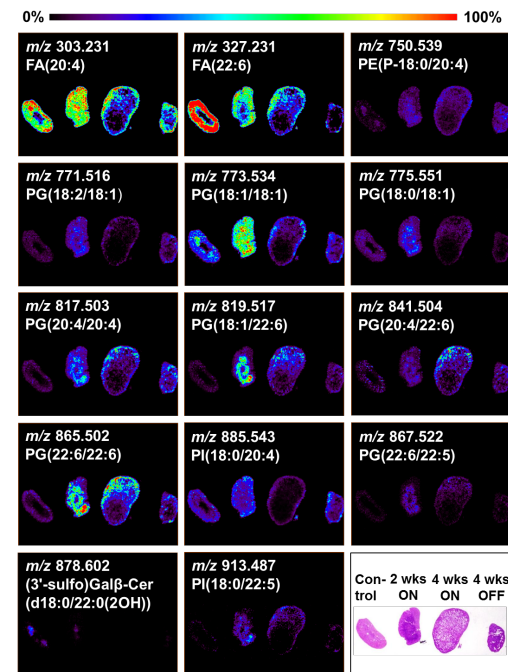
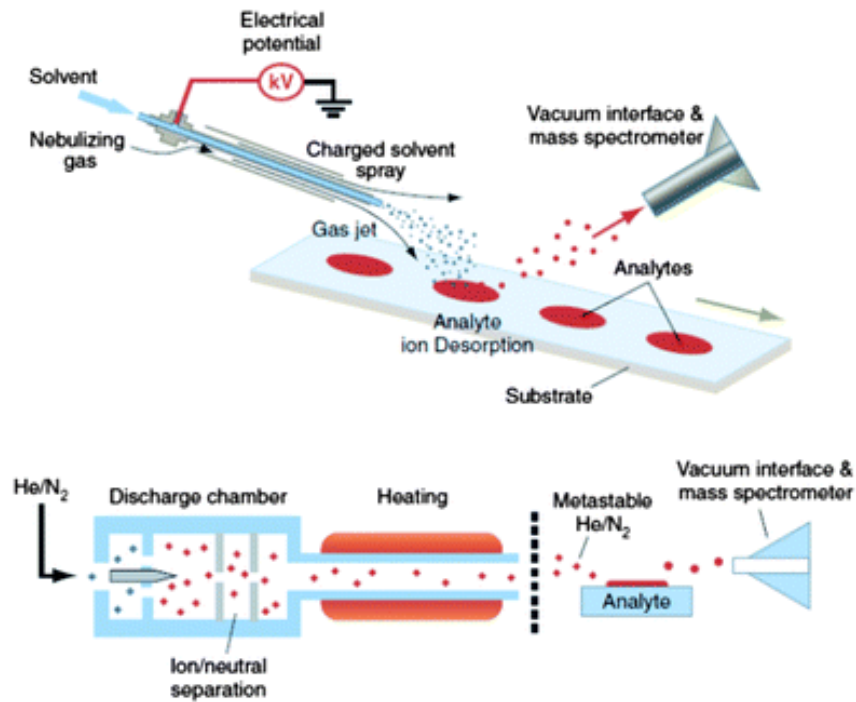


Nature Medicine 2009

Stanford University

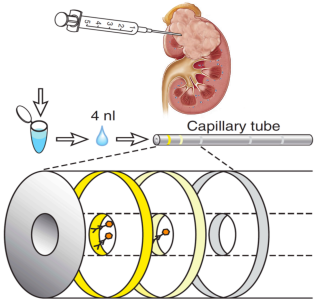
MYC and Lipogenesis

Felsher, Dang and Zare Labs

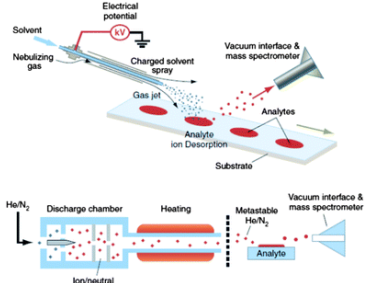
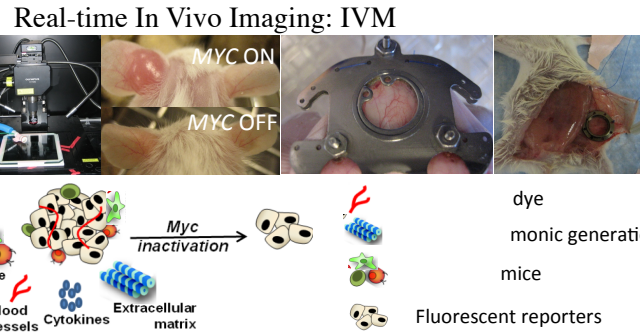
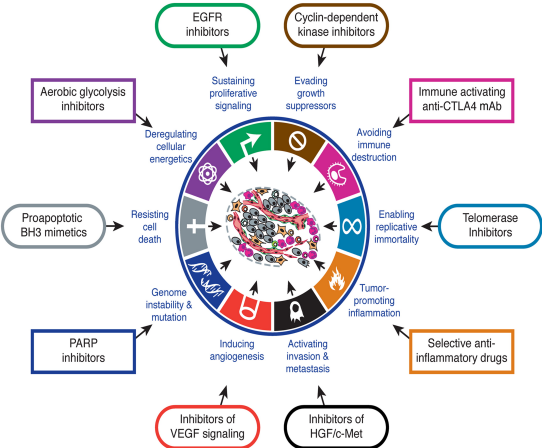


Gouw and Margulis *in revision*

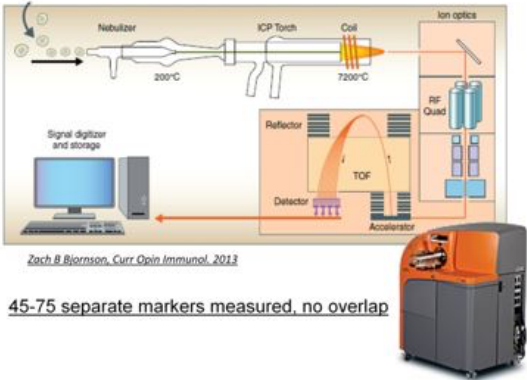
Cancer Hallmarks: Mechanisms, Diagnostics, and Therapeutics



MYC —



CyTOF (Cytometry by Time Of Flight)



45-75 separate markers measured, no overlap



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